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Preoperative platelet counts and postoperative outcomes in cancer surgery: a multicenter, retrospective cohort study

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Running head: Platelets and outcomes in cancer surgery

Abstract

Platelets play roles in malignancy, wound healing, and immunity. Nevertheless, their significance in postoperative outcomes is not established. This is a retrospective cohort study of 100,795 patients undergoing cancer surgery in 2010 and 2014 in >500 hospitals. Patients were stratified into five groups based on preoperative platelet counts. Multivariable logistic regression was used to determine the risk of 30-day mortality, morbidities, readmission, and prolonged hospitalization using the mid-normal group as a reference. We adjusted for demographic variables, comorbidities, and operation complexity. In the 2014 cohort, multivariable analysis showed that mortality was higher in patients with thrombocytopenia (OR 1.49, 95% CI [1.23-1.81]), high-normal platelets (OR 1.29, [1.06-1.55]), and thrombocytosis (OR 1.78, [1.45-2.19]). Composite postoperative morbidity followed a similar trend with thrombocytopenia (OR 1.34, [1.25-1.43]), high-normal counts (OR 1.41, [1.33-1.49]), and thrombocytosis (OR 2.20, [2.05-2.36]). Concordantly, the risks of prolonged hospitalization and 30-day readmission followed the same pattern. These results were validated in a large colon cancer cohort from the 2010 database. In conclusion, platelet count is a prognostic indicator in cancer surgeries. This could be related to the role of platelets in wound healing and immunity on one hand, and propagating malignancy on the other.

Keywords: Thrombocytes, oncology, mortality, morbidity

Introduction

Cancer patients are prone to alteration in their platelet counts due to the direct effect of cancer, chronic inflammatory state, or as a result of cancer therapy. Pretreatment platelet counts have been studied in a variety of cancers and high counts uniformly correlated with worse outcomes.[1, 2] Such studies have been limited by relatively small sample sizes, lack of generalizability, and confinement to specific cancer types and hospitals. On the other hand, platelets contribute to vital processes such as hemostasis, clearing infections, and wound healing.[3, 4] From a surgical standpoint, the significance of platelet counts in predicting potentially preventable post-operative morbidity and mortality has not been investigated. Of note, another blood count parameter, preoperative hemoglobin level, predicts postoperative morbidity and mortality.[5] This highlights the utility of such entities in identifying high risk surgical patients who are in this case undergoing cancer-related surgeries.

Preclinical studies provide ample evidence for the contribution of platelets to malignancy. We have shown that platelets promote cancer by suppressing adaptive anti-tumor immunity.[6] Moreover, platelets with deficient activation mechanisms are less likely to mediate metastasis.[7] Tumor cells in turn are capable of activating platelets, a process termed tumor cell-induced platelet aggregation (TCIPA), which engages platelets in protecting malignant cells from the immune system.[8] Thrombin derived from cancer cells stimulates their adhesion to platelets and promotes metastasis.[9] In fact, tumor ability for TCIPA correlates with its metastatic potential.[10] Platelets also release angiogenic factors such as VEGF and angiopoietin,[11, 12, 13]

promoting cancer nourishment, and can promote mitogenesis via a TGFβ-dependent mechanism.[14]

Cancer patients are also in a thrombophilic state as evidenced by thrombocytosis and elevated markers of platelet activation such as P-selectin in circulation, the latter of which correlates with venous thromboembolism.[15] Platelet microparticles (PMPs), released upon platelet activation, are elevated in cancer patients compared to controls and their level correlates with metastasis.[16] One mechanism promoting thrombopoiesis in malignancy involves IL-6-induced thrombopoietin production by the liver.[17]

Contrasting with their detrimental contributions to cancer, platelets have vital functions besides hemostasis. They participate in host defense against pathogens such as bacterial clearance from circulation through promoting their uptake by dendritic cells,[18] engulfment from Kuppfer cells,[19] or via release of cytokines with antimicrobial activities.[20] Given the state of immunosuppression which often complicates malignancy, such role for platelets in protection from pathogens could be particularly essential. Moreover, given that platelets are among the first cellular entities to arrive at the site of tissue injury, they have a major role in tissue healing and regeneration, via molecules such as platelet-derived growth factor (PDGF)[21] and stromal cell-derived factor-1.[4] Platelet-rich plasma is indeed used in osteoarthritis, a wear and tear process that can be reversed by the regenerative properties of platelets.[22]

In addition, platelets are qualitatively altered in the setting of cancer. Platelets from glioma and prostate cancer patients carry tumor-derived mutant RNA, and those from glioma patients have a distinct RNA signature compared to normal controls.[23] Given

the interaction between platelets and the immune system, it is conceivable that platelet count is often reflective of the systemic inflammatory state. Thus, cancer patients often show thrombocytosis secondary to this inflammatory milieu, or thrombocytopenia due to cancer-induced bone marrow suppression, platelet consumption by cancer-induced aggregation, or as a result of chemotherapy. Therefore, pre-operative platelet count could prove to be a useful, biologically sound indicator of the toll of cancer on these patients and their risk for future morbidities such as infections and thromboembolism.

In this study, we investigate the significance of preoperative platelet counts in predicting 30-day morbidity, mortality, and readmission, and total hospital length of stay in patients undergoing cancer surgeries across different cancer types. We analyze data from the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP) database. The NSQIP database is a well validated and robust patient registry. It resulted in tangible improvements in the performance of participating hospitals, including steady reductions in mortality and morbidity, as well as cutting healthcare expenses.[24, 25, 26, 27]

Methods

Study design

This is a retrospective cohort study analyzing data from the National Surgical Quality Improvement Program (NSQIP), which includes hundreds of voluntarily participating non-Veterans Affairs hospitals in the United States and international sites. These hospitals prospectively provide the NSQIP registry with data on patients undergoing major surgeries in the inpatient and outpatient settings. Data includes preoperative

medical conditions and lab values, intraoperative events, and postoperative morbidity and mortality until 30 days after surgery,[28] extending well beyond their discharge from the hospital. The purpose of this program is to provide continuous feedback to the participating hospitals to identify areas where improvement needs to be made. Data is collected by trained site Surgical Clinical Reviewers (SCRs) and transmitted to the national NSQIP registry. This information is collected directly from the patient's chart and if necessary, from phone calls and letters to patients. This data collection process is continuously subject to Inter-Rater Reliability Audit which ensures accurate data deposition.[29] Participating hospital training and audit procedures have ensured robust and effective data deposition in the NSQIP database.[28, 29, 30] This program has resulted in marked improvements in postoperative outcomes in the participating hospitals.[24, 25, 27]

In this study, we used the 2014 Participant Use Data File (PUF), which includes 750,397 cases from 517 hospitals. Cancer cases were then extracted using postoperative diagnosis ICD-9 codes (140-209.39 and 209.7-209.79), amounting to a total of 100,877 cases. Platelet count was available for 90,735 cases, which were used for analysis. For patients undergoing more than one surgery, the index case was used. To validate our findings, an independent cohort of 10,060 colon cancer patients was analyzed using the 2010 PUF.

Patients in the 2014 and 2010 datasets were divided into five categories based on their latest preoperative platelet count before the index surgery ($x10^3/\mu L$): <150 (I), 150-232 (II), 233-316 (III), 317-400 (IV) and >400 (V). These categories reflect thrombocytopenia (I), thrombocytosis (V), and the normal range divided into three equal intervals (II-IV).

Descriptive statistics were used to summarize baseline demographic variables, preoperative morbidities, and preoperative lab values (Table I).

The primary endpoints of this study were mortality and composite morbidity within 30 days from the date of surgery. Secondary endpoints included hospitalization for five or more days, readmission for any cause within 30 days from operation (available for the 2014 dataset only), and organ-specific morbidities within 30 days from surgery. Specific morbidities included: cardiac (myocardial infarction or cardiac arrest), respiratory (pneumonia, ventilator support >48h, or unplanned intubation), neurological (cerebrovascular accident), urinary (progressive renal insufficiency, acute renal failure, or urinary tract infection), wound complication (superficial, deep incisional/organ space surgical site infection, or wound dehiscence), hematological (blood transfusion within 72h postoperatively), sepsis, and venous thromboembolic (deep venous thrombosis or pulmonary embolism) events. Composite morbidity included the occurrence of any of the above specific morbidities. A comprehensive description of all variables is available in the ACS NSQIP Participant Use Data File (PUF) user guide (www.facs.org, 2017). There was no role for any funding source in the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit the article for publication.

Inclusion and exclusion criteria

This database includes major surgical cases in the inpatient and outpatient settings, as determined by their Current Procedural Terminology (CPT®) code, which is updated annually as new codes become available. Exclusion criteria consist of the following: patients under the age of 18 years, brain dead organ donors, cases involving

Hyperthermic Intraperitoneal Chemotherapy (HIPEC), trauma cases, and transplant cases (transplant procedure and any additional surgical procedure during the transplant hospitalization is excluded). To ensure diversity of collected cases, for programs other than small and rural hospitals, the database excludes cases beyond three per 8-day sampling cycle for the following procedures: inguinal herniorrhaphy, breast lumpectomy, laparoscopic cholecystectomy, transurethral resection of the prostate (TURP), and transurethral resection of bladder tumor (TURBT). Cases beyond the required number in a given site are also excluded. Returns to the operating room related to a complication of a prior procedure are also excluded, and so are multiple NSQIP assessed cases within 30 days: any patient who already has a NSQIP-assessed procedure entered within the previous 30 days.

Hospital exclusion criteria: To maintain a high level of data quality, only cases included in the hospital performance analysis are included in the PUF database analyzed in this study. Such cases go through another level of scrutiny which ensures their accuracy. A site is excluded if the 30-day follow-up rate is <80% or their Inter-Rater Reliability Audit disagreement is >5%.

Statistical analysis

For baseline variables (Table I), categorical variables were summarized with percentages and continuous variables were summarized with means and 95% confidence intervals. χ^2 and Analysis of Variance (ANOVA) tests were used for categorical and continuous variables, respectively. For outcome analysis, a univariate logistic regression was used to present the unadjusted odds ratios ($OR_{unadjusted}$) and associated 95% confidence intervals (CI) in which each outcome variable was

regressed on the group variable (platelet counts group) only. Second, to assess the risk factors for each outcome variable (30-day mortality, composite morbidity, hospital stay >5 days, and 30-day readmission), a logistic regression analysis was performed. In these models, each of the outcome variables was regressed on group variable and on each of the baseline variables, one at a time. Then a separate multiple logistic regression model was used for each outcome variable with adjusted odds ratios. Two levels of adjustment were used: OR1 (with 95% CI) is the adjusted odds ratio with basic adjustment for age, gender, race, work relative value unit, American Society of Anesthesiologists class, and functional status. OR2 (with 95% CI) is the adjusted odds ratio with further adjustment of comorbidities and clinically relevant variables besides adjusting for covariates in OR1 (Supplementary table I). Data for this study was nearly complete for all variables, except for a fraction of preoperative lab values (Supplementary table II). Lastly, we fit a separate stratified multiple logistic regression model for each outcome with adjustment: OR2 is the odds ratio (with 95% CI) in which we regress each outcome on the above-mentioned basic covariates (in OR1) and additional clinically relevant covariates (Supplementary table I). All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, North Carolina).

Results

Baseline variables

The 2014 cohort included 90,735 patients with known platelet counts. The mean age was 62.53 (±13.42) years and 56.07% were females. The majority of patients (90.9%) had platelet counts within a month before surgery. Patients were divided into five

categories based on platelet counts: thrombocytopenia (I), low-normal (II), mid-normal (III), high-normal (IV), and thrombocytosis (V) (Table I). Groups I, IV, and V constituted 24.87% of the patients and were more likely to have comorbidities.

Lower platelet counts were associated with older age, male gender, a co-existing bleeding disorder, diabetes mellitus requiring medication, and chronic steroid use. Higher platelet counts (groups IV and V) were associated with tobacco use, infected surgical wounds, and sepsis in the 48 hours preceding surgery.

Patients with thrombocytopenia or thrombocytosis were less likely to be in ASA classes I and II, had slightly more complex cases (as indicated by RVU), and had longer operation times. They were also more likely to have weight loss >10%, BMI <18.5, disseminated cancer, and albumin <35 g/L.

Groups I, IV, and V were more likely to spend one or more days in the hospital prior to surgery, receive a preoperative transfusion, and to have abnormal preoperative lab values.

Table I also includes the frequencies of the seven most common cancers in the US. Cancer types were differentially distributed among platelet groups; for example, prostate cancer was more likely to associate with lower platelet counts than colon cancer.

Preoperative platelet counts predict postoperative morbidity, mortality, hospital length of stay, and readmission rate in the 2014 cohort

Group III was used as a reference to estimate the significance of platelets across the whole range of platelet counts. Crude mortality, composite morbidity, readmission within 30 days, and hospitalization for at least five days (above the average) were all higher in

groups I, IV, and V (Table II). This pattern persisted after adjusting for comorbidities and possible confounders in models 1 and 2 (Supplementary table I). When specific morbidities were investigated, a similar trend was observed. This included cardiac, respiratory, neurological, urinary, wound, infectious, venous thromboembolic, and hematological morbidities, all uniformly showing increased risk in categories I, IV, and V (Table II).

Platelet prognostic significance stratified by age, gender, and cancer dissemination

Patients were stratified by age (<65 or ≥65 years), gender, and cancer status (disseminated or regional/local). To further dissect the role of platelets in dictating/predicting postoperative outcomes, we adjusted for additional variables such as postoperative diagnosis (PODIAG) and preoperative hematocrit (PRHCT). Extensively adjusting for variables is often unnecessary and can lead to over-adjustment bias.[31] Regarding postoperative diagnosis, this is particularly true since the significance of platelets should be tested in individual cancer types, regardless of adjusting in the current analysis. As for hematocrit, its level can be associated with platelet count either in a causal or bystander manner. However, in the stratified analysis (Table III), PODIAG and PRHCT were included in the adjustment models for more conservative observations. Stratifying patients by age, gender, and cancer dissemination, the association of platelets with outcomes persisted. Univariate and multivariate analyses showed that 30-day mortality was higher in groups I and V, and composite morbidity was increased in groups I, IV, and V (Table III).

Platelets in colon cancer: a validation dataset

The above analyses were based on the 2014 NSQIP cohort. To validate the utility of platelet counts in predicting outcomes, an independent NSQIP cohort from a different year (2010) was analyzed, where all the patients had surgeries with a postoperative diagnosis of colon cancer (Table IV). Colon cancer was chosen because it included the highest number of cases with a relatively balanced distribution of both genders in the 2010 NSQIP database. This database included additional baseline variables which were not available in the 2014 one: preoperative cerebrovascular accidents, chemotherapy within 30 days before surgery, radiation therapy in the preceding 90 days, and alcohol >2 drinks/day in the two weeks preceding admission. These variables were adjusted for in model 2. Readmission data were not available for the 2010 cohort.

Colon cancer patients with thrombocytopenia or thrombocytosis constituted 16.16% of the whole colon cancer patient population, yet, they accounted for 33.95% of the deaths (Table IV). Mortality and composite morbidity were more prevalent in groups I and V, and this increased risk persisted after adjusting for confounders in models 1 and 2. Patients in groups I, IV, and V were also more likely to be hospitalized for at least five days, which also persisted after adjusting for confounders (Table IV, supplementary table I). This supports the above findings where platelets are an independent predictor of morbidity and mortality in colon cancer patients.

Discussion

This multicenter study is the first to establish an association between preoperative platelet counts and postoperative outcomes in a large cohort of patients. It provides an insight into platelets whose clinical role beyond hemostasis is very little appreciated.

Higher platelet counts have been associated with more aggressive cancers.[1, 2] This is potentially related to the increased inflammatory environment associated with malignancy which is known to induce thrombopoiesis, or the contribution of platelets to cancer invasiveness and thrombophilia. There is evidence that platelets also play roles in tissue regeneration[4, 22] and fighting infections,[3] although human studies are still lacking. Our findings of superior postoperative outcomes in patients with platelets in the low- and mid-normal ranges are consistent with the above premises.

Anemia has been shown to predict worse postoperative outcomes in noncardiac surgery.[5] Patients in categories I, IV, and V were more likely to be anemic in this study. Chronic inflammation often results in both anemia and thrombopoiesis, and anemia in turn can induce platelet production, all resulting in increased anemia prevalence in groups IV and V. On the other hand, cancer or therapy-induced bone marrow suppression or consumptive coagulopathy can induce anemia and thrombocytopenia, explaining the higher prevalence of anemia in group I. Nevertheless, adjusting for preoperative transfusions and anemia of any severity showed that platelets independently predicted outcomes regardless of anemia status (Table III).

This study comprises a large number of patients from hundreds of hospitals including international sites, relies on a robust, prospective data collection as evidenced by strict quality measures and validation studies, and thoroughly adjusts for comorbidities that are provided in the ACS NSQIP database. Our study also bears some limitations: 1) Patient follow-up is until 30 days and thus, complications and death beyond that period are not recorded. 2) The data is deposited by NSQIP participating hospitals, and does not necessarily represent other non-participating facilities. 3) Around 9% of the patients

had their platelet counts >28 days from time of surgery and that might not represent the numbers shortly before operation. 4) The observational nature of the study cannot establish a causal relationship between platelet counts and outcomes. Importantly, mean platelet volume (MPV) and platelet distribution width (PDW) can provide insight into platelet function beyond platelet counts. Indeed, recent studies demonstrated a prognostic value of these parameters in different types of cancer.[32, 33, 34, 35] Therefore, it is imperative that future studies address the significance of platelet parameters besides their counts in predicting postoperative outcomes. Data on MPV and PDW are not available in the NSQIP database.

Conclusions

This work shows that both low and high platelet counts are independent predictors of increased mortality in cancer surgery. Even patients with normal platelet counts have an increased risk if their counts are in the upper third of the normal range. Platelet counts also uniformly predicted hospitalization time, 30-day readmission, and specific

morbidities. This is true in younger and elderly patients, both genders, and regardless of cancer metastasis. Importantly, these findings were validated in an independent, large, multicenter cohort of colon cancer patients. Future studies should investigate treating patients with platelet products or antiplatelet drugs as the role of platelets besides hemostasis is increasingly recognized.

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Table I. Baseline variables and preoperative comorbidities in the 2014 cohort. [a]Cardiac, gynecology, neurosurgery, orthopedics, otolaryngology, plastics, thoracic, urology, vascular, and interventional radiology. [b]Transfusion within 72 hours before surgery. RVU: Relative Value Unit; a measure implemented by the US Medicare to determine reimbursement based on case complexity. ASA: American Society of Anesthesiologists; classes range from I to VI. I: Healthy; II: mild systemic disease; III: severe systemic disease, IV: severe systemic life threatening disease; V: moribund and will not survive without the surgery; VI: dead. CI: Confidence Interval. COPD: Chronic Obstructive Pulmonary Disease. Platelet groups were compared using χ^2 test for categorical variables and Analysis of Variance (ANOVA) for continuous variables. All variables showed statistical difference among groups with $p<0.0001$, except acute renal failure ($p=0.19$). Given the large number of patients, the differences among platelet groups were often statistically significant despite being small and not necessarily clinically significant.

Baseline Variables\Platelet Count ($x10^3/\mu L$)	**(I) <150 n=6,378 (7.03 %)**	**(II) 150-232 n=34,794 (38.35 %)**	**(III) 233-316 n=33,371 (36.78 %)**	**(IV) 317-400 n=11,192 (12.33 %)**	**(V) >400 n=5,000 (5.51 %)**
Age ≥65 years (%)	56.08	49.97	43	42.29	42.26
Sex (female)	37.97	47.15	63.02	69.33	65.28
Race (white)	79.84	77.75	76.87	75.04	73.68
Surgical subspecialty					
General	58.44	53.74	57.98	61.93	64.50
Other[a]	41.56	46.26	42.02	38.08	35.50

Work RVU, mean [95% CI]	25.09 [24.77-25.42]	23.87 [23.75-24.00]	23.02 [22.90-23.15]	23.52 [23.30-23.73]	25.35 [25.04-25.67]
General anesthesia	97.04	97.24	97.35	97.59	98.66
ASA class					
I–II	25.63	40.72	44.50	40.90	32.70
III	63.99	53.86	50.99	53.86	59.40
IV–V	10.16	5.22	4.32	5.03	7.80
Infected surgical wound class	1.38	0.90	1.18	2.41	6.14
Total operation time, mean [95% CI]	194.97 (191.55-198.40)	184.15 (182.80-185.49)	179.51 (178.17-180.86)	180.64 (178.29-182.99)	193.00 (189.25-196.75)
Inpatient status	79.52	73.55	70.80	74.86	86.76
Days from admission to operation					
0	86.12	90.95	90.70	86.67	78.34
1	3.67	2.81	2.92	3.52	6.00
>1	10.21	6.24	6.38	9.81	15.66
Emergency case	2.23	1.47	1.75	3.21	5.74
Preoperative transfusion[b]	2.59	0.95	0.96	2.13	4.60
Functional status					
Independent	97.12	98.08	98.11	97.73	96.46
Partially dependent	2.10	1.33	1.34	1.72	2.82
Dependent	0.34	0.18	0.17	0.29	0.42

Cardiovascular variables					
Dyspnea					
None	91.28	93.43	93.24	91.74	89.84
With moderate exertion	8.03	6.18	6.36	7.61	9.30
At rest	0.69	0.40	0.40	0.65	0.86
Congestive heart failure in previous 30 days	1.27	0.71	0.50	0.52	0.66
Hypertension requiring medication	55.33	51.51	49.58	49.24	47.28
Respiratory variables					
Tobacco use in past year	15.58	14.72	16.65	19.03	21..02
History of severe COPD	6.30	5.19	5.22	6.48	6.46
Ventilator-dependent in previous 48 h	0.33	0.11	0.07	0.13	0.22
Hepatobiliary variables					
Ascites in 30 previous days	1.30	0.42	0.80	1.70	5.24
Renal variables					
Acute renal failure	0.22	0.16	0.13	0.14	0.24
Presently on dialysis	1.32	0.58	0.32	0.21	0.30
Hemato-oncological variables					
Bleeding disorder	11.52	2.57	1.81	1.82	2.90
Weight loss >10% in previous 6 months	5.08	3.17	3.78	6.13	12.56
Disseminated cancer	18.89	11.73	10.76	15.12	24.22

Other variables					
Body-mass index					
<18.5	2.82	2.12	2.39	3.37	6.30
18.5-30	62.70	61.54	59.52	60.59	63.52
>30	34.48	36.34	38.10	36.04	30.18
Diabetic on oral drugs or insulin	8.45	5.62	5.38	5.92	5.88
Open wound (with or without infection)	1.24	0.78	0.84	1.19	2.26
Steroid use for chronic condition	6.19	3.75	3.44	3.96	3.82
Systemic sepsis in previous 48 h	2.45	1.21	1.39	2.84	8.12
Days from platelet measurement to operation					
0-14	77.39	74.47	74.26	75.85	82.74
15-28	14.08	16.04	16.45	15.12	11.34
29-56	6.60	7.29	7.08	6.92	4.70
57+	1.93	2.20	2.22	2.11	1.22
Preoperative lab values					
Na<136 mmol/L	10.73	7.80	9.35	14.42	22.68
Na>145 mmol/L	2.03	1.64	1.37	1.13	0.97
Creatinine <61.9 μmol/L	16.41	15.85	21.17	25.59	28.73
Creatinine >132.6 μmol/L	8.77	5.21	3.84	3.84	3.88
BUN <2.9 mmol/L	5.57	4.20	5.37	7.91	12.28
BUN >7.1 mmol/L	25.88	21.26	16.94	15.98	14.73
Albumin <35 g/L	24.41	13.12	13.88	23.22	43.72

Albumin >55 g/L	0.15	0.06	0.05	0.14	0.10
Total Bilirubin <5.1 µmol/L	5.60	6.67	10.42	15.13	18.44
Total Bilirubin >17.1 µmol/L	17.07	9.03	6.81	7.08	8.38
AST <10 U/L	1.09	1.18	1.36	1.91	2.70
AST >40 U/L	20.55	9.63	8.21	9.80	13.05
Alk Phos <30 U/L	0.47	0.39	0.49	0.31	0.33
Alk Phos >120 U/L	19.15	10.50	11.43	16.11	26.08
WBC <4,000 cells/µL	18.37	6.28	2.87	1.67	0.76
WBC >10.000 cells/µL	6.77	6.90	12.68	22.42	40.25
INR >1.2	11.51	5.93	5.37	7.36	13.34
HCT <35%	30.97	16.45	17.95	30.69	56.58
HCT>50%	0.74	0.92	0.47	0.34	0.32
PTT <25 s	11.53	11.26	10.90	11.72	10.89
PTT >35 s	14.45	8.99	8.68	11.02	16.12
Cancer type					
Trachea, bronchus and lung	4.12	4.02	4.12	4.15	4.10
Breast	11.30	17.50	22.63	20.03	8.46
Prostate	6.71	10.65	6.52	3.02	1.20
Colorectal	18.17	18.21	19.53	24.57	35.36
Uterus	2.09	4.43	6.84	7.53	6.48
Melanoma	0.83	0.74	0.61	0.29	0.24
Bladder	9.11	6.84	4.67	3.76	3.24
Other	47.66	37.61	35.07	36.64	40.92

Table II. Mortality, morbidity, hospitalization time, and readmission rates in the 2014 cohort. Data includes odds ratios (OR) and 95% confidence intervals (CI). OR1 and OR2 adjust for variables indicated in supplementary table 1.

Outcomes\Platelet Count ($x10^3/\mu L$)	**(I) <150 n=6,378 (7.03 %)**	**(II) 150-232 n=34,794 (38.35 %)**	**(III) 233-316 n=33,371 (36.78 %)**	**(IV) 317-400 n=11,192 (12.33 %)**	**(V) >400 n=5,000 (5.51 %)**
30-day mortality					
Count (%)	183 (2.87)	410 (1.18)	344 (1.03)	175 (1.56)	148 (2.96)
$OR_{unadjusted}$	2.84 (2.37-3.40	1.14 (0.99-1.32)	1.00	1.53 (1.27-1.83)	2.93 (2.41-3.56)
OR1	1.72 (1.43-2.07)	0.95 (0.82-1.10)	1.00	1.48 (1.23-1.78)	2.41 (1.97-2.94)
OR2	1.49 (1.23-1.81)	0.98 (0.84-1.13)	1.00	1.29 (1.06-1.55)	1.78 (1.45-2.19)
Composite morbidity					
Count (%)	1689 (26.48)	5773 (16.59)	5369 (16.09)	2518 (22.5)	1794 (35.88)
$OR_{unadjusted}$	1.88 (1.76-2.00)	1.04 (1.00-1.08)	1.00	1.51 (1.44-1.60)	2.92 (2.74-3.11)
OR1	1.45 (1.36-1.55)	0.94 (0.90-0.98)	1.00	1.50 (1.42-1.59)	2.64 (2.46-2.82

OR2	1.34 (1.25-1.43)	0.95 (0.90-0.99)	1.00	1.41 (1.33-1.49)	2.20 (2.05-2.36)
Readmission within 30 days					
Count (%)	703 (11.10)	2850 (8.28)	2617 (7.91)	1013 (9.11)	565 (11.37)
$OR_{unadjusted}$	1.45 (1.33-1.59)	1.05 (0.99-1.11)	1.00	1.17 (1.08-1.26)	1.49 (1.36-1.64)
OR1	1.21 (1.11-1.32)	0.98 (0.93-1.04)	1.00	1.15 (1.07-1.24)	1.36 (1.23-1.50)
OR2	1.13 (1.04-1.24)	0.99 (0.93-1.04)	1.00	1.11 (1.03-1.20)	1.23 (1.11-1.36)
Hospital stay ≥5 days					
Count (%)	2,986 (46.89)	12,250 (35.24)	11,054 (33.15)	4,571 (40.89)	2,930 (58.67)
$OR_{unadjusted}$	1.78 (1.69-1.88)	1.10 (1.06-1.13)	1.00	1.40 (1.34-1.46)	2.86 (2.69-3.04)
OR1	1.25 (1.18-1.34)	0.92 (0.89-0.96)	1.00	1.47 (1.40-1.55)	2.80 (2.61-3.00)
OR2	1.14 (1.06-1.22)	0.94 (0.90-0.98)	1.00	1.34 (1.27-1.42)	2.14 (1.99-2.31)
Specific Morbidities					
Cardiac					
Count (%)	81 (1.27)	307 (0.88)	211 (0.63)	86 (0.77)	61 (1.22)

$OR_{unadjusted}$	2.02 (1.56-2.62)	1.40 (1.17-1.67)	1.00	1.22 (0.95-1.57)	1.94 (1.46-2.58)
OR1	1.29 (1.00-1.68)	1.17 (0.98-1.40)	1.00	1.18 (0.92-1.53)	1.63 (1.22-2.17)
OR2	1.22 (0.94-1.59)	1.19 (1.00-1.42)	1.00	1.13 (0.88-1.46)	1.49 (1.12-2.00)
Respiratory					
Count (%)	363 (5.69)	1050 (3.02)	882 (2.64)	436 (3.90)	253 (5.06)
$OR_{unadjusted}$	2.22 (1.96-2.52)	1.15 (1.05-1.26)	1.00	1.49 (1.33-1.68)	1.96 (1.70-2.27)
OR1	1.45 (1.28-1.65)	0.97 (0.89-1.07)	1.00	1.46 (1.30-1.65)	1.63 (1.41-1.89)
OR2	1.36 (1.19-1.55)	1.00 (0.91-1.09)	1.00	1.34 (1.19-1.52)	1.37 (1.18-1.59)
CNS					
Count (%)	23 (0.36)	81 (0.23)	71 (0.21)	34 (0.30)	24 (0.48)
$OR_{unadjusted}$	1.70 (1.06-2.72)	1.09 (0.80-1.51)	1.00	1.43 (0.95-2.15)	2.26 (1.42-3.60)
OR1	1.19 (0.74-1.91)	0.96 (0.69-1.32)	1.00	1.39 (0.92-2.09)	1.95 (1.22-3.11)
OR2	1.16 (0.71-1.87)	0.97 (0.70-1.34)	1.00	1.33 (0.88-2.01)	1.80 (1.13-2.88)
Urinary					

Count (%)	283 (4.44)	963 (2.77)	799 (2.39)	355 (3.17)	162 (3.24)
$OR_{unadjusted}$	1.89 (1.65-2.17)	1.16 (1.06-1.28)	1.00	1.34 (1.18-1.52)	1.37 (1.15-1.62)
OR1	1.49 (1.30-1.72)	1.07 (0.97-1.18)	1.00	1.28 (1.13-1.46)	1.17 (0.99-1.40)
OR2	1.41 (1.22-1.63)	1.08 (0.98-1.19)	1.00	1.23 (1.08-1.40)	1.05 (0.88-1.24)
Wound					
Count (%)	480 (7.53)	2044 (5.87)	1931 (5.79)	837 (7.48)	549 (10.98)
$OR_{unadjusted}$	1.33 (1.19-1.47)	1.02 (0.95-1.08)	1.00	1.32 (1.21-1.43)	2.01 (1.82-2.22)
OR1	1.08 (0.97-1.20)	0.95 (0.89-1.01)	1.00	1.28 (1.17-1.39)	1.78 (1.61-1.97)
OR2	1.04 (0.93-1.16)	0.96 (0.89-1.02)	1.00	1.23 (1.13-1.34)	1.55 (1.39-1.71)
Sepsis					
Count (%)	322 (5.05)	1051 (3.02)	914 (2.74)	467 (4.17)	338 (6.76)
$OR_{unadjusted}$	1.89 (1.66-2.15)	1.11 (1.01-1.21)	1.00	1.55 (1.38-1.73	2.58 (2.27-2.93)
OR1	1.31 (1.14-1.50)	0.96 (0.87-1.05)	1.00	1.52 (1.35-1.70)	2.20 (1.92-2.51)
OR2	1.21 (1.05-1.39)	0.98 (0.89-1.07)	1.00	1.36 (1.21-1.53)	1.57 (1.37-1.80)

Venous Thromboembolic					
Count (%)	145 (2.27)	484 (1.39)	470 (1.41)	206 (1.84)	147 (2.94)
$OR_{unadjusted}$	1.63 (1.35-1.97)	0.99 (0.87-1.12)	1.00	1.31 (1.11-1.55)	2.12 (1.76-2.56)
OR1	1.23 (1.02-1.49)	0.89 (0.78-1.02)	1.00	1.28 (1.08-1.51)	1.85 (1.53-2.23)
OR2	1.13 (0.93-1.37)	0.89 (0.78-1.01)	1.00	1.20 (1.02-1.42)	1.56 (1.28-1.88)
Intra/post-operative transfusion					
Count (%)	972 (15.24)	2602 (7.48)	2493 (7.47)	1325 (11.84)	1210 (24.20)
$OR_{unadjusted}$	2.23 (2.06-2.41)	1.00 (0.95-1.06)	1.00	1.66 (1.55-1.78)	3.95 (3.66-4.27)
OR1	1.74 (1.60-1.90)	0.92 (0.87-0.98)	1.00	1.61 (1.49-1.73)	3.54 (3.27-3.84)
OR2	1.56 (1.43-1.70)	0.92 (0.86-0.97)	1.00	1.50 (1.39-1.61)	2.89 (2.66-3.14)

Table III. Stratified analysis by age, gender, and cancer dissemination status (2014). Data includes OR and 95% CI. OR1 and OR2 adjust for variables indicated in supplementary table 1.

Outcomes\Platelet Count ($x10^3/\mu L$)	**(I) <150 n=6,378 (7.03 %)**	**(II) 150-232 n=34,794 (38.35 %)**	**(III) 233-316 n=33,371 (36.78 %)**	**(IV) 317-400 n=11,192 (12.33 %)**	**(V) >400 n=5,000 (5.51 %)**
30-day mortality					
Age					
<65 years (n=48,579)					
$OR_{unadjusted}$	4.77 (3.41-6.68)	1.34 (1.01-1.79)	1.00	1.55 (1.07-2.23)	4.14 (2.92-5.86)
OR2	1.95 (1.36-2.79)	1.18 (0.88-1.58)	1.00	1.16 (0.79-1.68)	1.57 (1.09-2.28)
≥65 years (n=42,156)					
$OR_{unadjusted}$	1.96 (1.58-2.44)	0.97 (0.82-1.15)	1.00	1.54 (1.25-1.91)	2.58 (2.03-3.27)
OR2	1.23 (0.98-1.55)	0.93 (0.78-1.10)	1.00	1.22 (0.98-1.53)	1.48 (1.15-1.90)
Sex					
Male (n=39,856)					
$OR_{unadjusted}$	2.02 (1.61-2.54)	0.96 (0.80-1.16)	1.00	1.62 (1.25-2.09)	2.64 (2.00-3.49)

OR2	1.42 (1.12-1.81)	0.99 (0.82-1.20)	1.00	1.23 (0.94-1.60)	1.45 (1.08-1.94)
Female (n=50,879)					
$OR_{unadjusted}$	3.51 (2.60-4.75)	1.13 (0.89-1.43)	1.00	1.60 (1.23-2.09)	3.39 (2.57-4.46)
OR2	1.42 (1.03-1.98)	0.97 (0.76-1.23)	1.00	1.19 (0.91-1.57)	1.60 (1.20-2.15)
Cancer Dissemination					
Local (n=78,954)					
$OR_{unadjusted}$	2.81 (2.21-3.56)	1.20 (1.00-1.44)	1.00	1.38 (1.08-1.76)	2.45 (1.85-3.23)
OR2	1.47 (1.14-1.88)	1.00 (0.83-1.21)	1.00	1.18 (0.92-1.51)	1.44 (1.08-1.92)
Disseminated (n=11,781)					
$OR_{unadjusted}$	1.89 (1.42-2.52)	0.99 (0.78-1.26)	1.00	1.34 (1.01-1.78)	1.93 (1.45-2.57)
OR2	1.38 (1.01-1.88)	1.01 (0.78-1.30)	1.00	1.21 (0.89-1.63)	1.54 (1.13-2.08)
Composite morbidity					
Age					
<65 years (n=48,579)					
$OR_{unadjusted}$	2.18 (1.98-2.39)	1.07 (1.01-1.14)	1.00	1.52 (1.41-1.63)	3.22 (2.95-3.51)

OR2	1.30 (1.17-1.44)	0.98 (0.92-1.05)	1.00	1.30 (1.20-1.41)	1.83 (1.66-2.02)
≥65 years (n=42,156)					
$OR_{unadjusted}$	1.56 (1.43-1.69)	0.96 (0.91-1.02)	1.00	1.53 (1.42-1.65)	2.65 (2.41-2.92)
OR2	1.20 (1.09-1.31)	0.94 (0.88-1.00)	1.00	1.27 (1.16-1.38)	1.58 (1.42-1.76)
Sex					
Male (n=39,856)					
$OR_{unadjusted}$	1.47 (1.36-1.60)	0.92 (0.87-0.97)	1.00	1.57 (1.44-1.71)	2.66 (2.39-2.96)
OR2	1.21 (1.11-1.33)	0.95 (0.89-1.01)	1.00	1.31 (1.20-1.44)	1.76 (1.57-1.97)
Female (n=50,879)					
$OR_{unadjusted}$	2.16 (1.95-2.38)	1.04 (0.98-1.10)	1.00	1.56 (1.46-1.67)	3.19 (2.93-3.46)
OR2	1.29 (1.15-1.44)	0.97 (0.91-1.03)	1.00	1.27 (1.18-1.37)	1.69 (1.54-1.85)
Cancer Dissemination					
Local (n=78,954)					
$OR_{unadjusted}$	1.89 (1.76-2.03)	1.06 (1.01-1.11)	1.00	1.45 (1.37-1.54)	2.84 (2.64-3.06)

OR2	1.28 (1.18-1.38)	0.97 (0.93-1.02)	1.00	1.25 (1.17-1.33)	1.71 (1.57-1.86)
Disseminated (n=11,781)					
$OR_{unadjusted}$	1.35 (1.18-1.55_	0.89 (0.81-0.98)	1.00	1.48 (1.31-1.67)	2.10 (1.83-2.40)
OR2	1.13 (0.98-1.31)	0.90 (0.81-1.00)	1.00	1.37 (1.21-1.56)	1.63 (1.42-1.89)

Table IV. Platelet counts predict outcomes in the year of 2010 validation dataset of colon cancer patients. Data includes OR and 95% CI. OR1 and OR2 adjust for variables indicated in supplementary table 1.

Outcomes\Platelet Count ($x10^3/\mu L$)	**(I) <150 n=660 (6.56 %)**	**(II) 150-232 n=3,446 (34.25 %)**	**(III) 233-316 n=3,500 (34.79 %) Reference**	**(IV) 317-400 n=1,488 (14.79 %)**	**(V) >400 n=966 (9.60 %)**
30-day mortality					
Count (%)	35 (5.30)	71 (2.06)	46 (1.31)	27 (1.81)	39 (4.04)
$OR_{unadjusted}$	4.20 (2.69-6.58)	1.58 (1.09-2.30)	1.00	1.39 (0.86-2.24)	3.16 (2.05-4.87)
OR1	2.66 (1.66-4.25)	1.36 (0.93-2.00)	1.00	1.21 (0.74-1.97)	2.76 (1.76-4.33)
OR2	2.51 (1.54-4.08)	1.43 (0.97-2.11)	1.00	1.18 (0.72-1.93)	2.33 (1.47-3.69)
Composite morbidity					
Count (%)	229 (34.70)	913 (26.49)	915 (26.14)	427 (28.70)	379 (39.23)
$OR_{unadjusted}$	1.50 (1.26-1.79)	1.02 (0.92-1.13)	1.00	1.14 (0.99-1.30)	1.82 (1.57-2.12)
OR1	1.29 (1.07-1.55)	0.96 (0.86-1.07)	1.00	1.09 (0.95-1.25)	1.74 (1.49-2.03)

OR2	1.22 (1.01-1.47)	0.95 (0.85-1.07)	1.00	1.08 (0.94-1.25)	1.67 (1.43-1.95)
Hospital stay ≥5 days					
Count (%)	514 (78.23)	2435 (70.74)	2493 (71.35)	1125 (75.91)	761 (79.11)
$OR_{unadjusted}$	1.44 (1.18-1.76)	0.97 (0.88-1.08)	1.00	1.27 (1.10-1.46)	1.52 (1.28-1.80)
OR1	1.25 (1.01-1.54)	0.91 (0.81-1.01)	1.00	1.23 (1.06-1.42)	1.48 (1.24-1.76)
OR2	1.18 (0.96-1.46)	0.89 (0.80-0.99)	1.00	1.20 (1.04-1.39)	1.39 (1.16-1.67)

Supplementary material for Rachidi et al. "Preoperative platelet counts and postoperative outcomes in cancer surgery: a multicenter, retrospective cohort study".

Supplementary table I. Baseline variables adjusted for in the regression models. [a]OR1 2010 and 2014. [b]OR2 2014. [c]OR2 2014 stratified. [d]OR2 2010. *Variable available in 2010 dataset only. [#]Outcome available in 2014 dataset only.

Baseline Variable\Outcome Variable	Mortality	Overall Complications	Cardiac	Resp	CNS	Urinary	Wound	Sepsis	Venous	Intra/postop transfusion	Hospitalization Time	30-day Readmission #
Age	a,b,c,d	a,b,c,d	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c
Sex	a,b,c,d	a,b,c,d	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c
Race	a,b,c,d	a,b,c,d	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c
ASA class	a,b,c,d	a,b,c,d	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c
Inpatient status	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Preoperative transfusion	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Functional status	a,b,c,d	a,b,c,d	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c
History of CHF	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Dyspnea				b,c								
Hypertension requiring medication			b,c		b,c							
Tobacco use in past year	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
History of COPD	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Ventilator-dependent in previous 48h				b,c				b,c				
Renal failure	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Bleeding disorder	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c

Table continued

Disseminated cancer	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Diabetic on oral hypoglycemic or insulin	b,c,d	b,c,d	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c	b,c,d	b,c
Wound class							b,c	b,c				
Steroid use							b,c	b,c		b,c		
Preoperative sepsis							b,c	b,c				
Preoperative hematocrit	c	c									c	c
Postoperative diagnosis	c	c									c	c
Work RVU	a,b,c,d	a,b,c,d	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c
Ethanol >2 drinks/day in 2 weeks before admission*	d	d									d	
CVA with neurological deficit*	d	d									d	
CVA without neurological deficit*	d	d									d	
Radiotherapy in the last 90 days*	d	d									d	
Chemotherapy in 30 days before surgery*	d	d									d	

Supplementary Table II. Frequencies of missing variables in the 2014 database.

Variable	Count missing (% of analyzed patients)
Age	0
Sex	0
Race	0
Surgical subspecialty	0
Work RVU	0
Type of anesthesia	0
ASA class	0
Wound class	0
Total operation time	0
Inpatient/outpatient status	0
Days from admission to operation	0
Emergency case	0
Preoperative transfusion	0
Functional status	0
Dyspnea	0
Congestive heart failure in previous 30 days	0
Hypertension requiring medication	0
Tobacco use in past year	0
History of severe COPD	0
Ventilator-dependent in previous 48 h	0

Table continued

Ascites in previous 30 days	0
Acute renal failure	0
Presently on dialysis	0
Bleeding disorder	0
Weight loss >10% in previous 6 months	0
Disseminated cancer	0
Body-mass index	0
Diabetic on oral drugs or insulin	0
Open wound (with or without infection)	0
Steroid use for chronic condition	0
Systemic sepsis in previous 48 h	0
Days from platelet measurement to operation	0
Serum sodium	4,429 (4.88)
Serum creatinine	3,172 (3.50)
BUN	7,245 (7.99)
Albumin	28,028 (30.89)
Total bilirubin	28,213 (31.09)
AST	28,207 (31.09)
Alkaline phosphatase	27,832 (30.67)
WBC	207 (0.23)
INR	42,754 (47.12)
HCT	194 (0.02)
PTT	51,838 (57.13)